Control of Blood Pressure and Risk of Stroke Among Pharmacologically Treated Hypertensive Patients

Olaf H. Klungel, PharmD, PhD; Robert C. Kaplan, MS, PhD; Susan R. Heckbert, MD, PhD; Nicholas L. Smith, MPH, PhD; Rozenn N. Lemaitre, MPH, PhD; W.T. Longstreth, Jr, MD, MPH; Hubert G.M. Leufkens, PharmD, PhD; Anthonius de Boer, MD, PhD; Bruce M. Psaty, MD, PhD

Background and Purpose—Despite improved control of blood pressure during the last decades in the United States, a considerable proportion of treated hypertensives have not achieved target blood pressure levels. We estimated the proportion of strokes occurring among treated hypertensive patients that may be attributable to uncontrolled blood pressure.

Methods—A population-based case-control study was conducted among treated hypertensive members of Group Health Cooperative of Puget Sound. Cases were treated hypertensive patients who sustained a first fatal or nonfatal, ischemic (n=460) or hemorrhagic (n=95) stroke during 1989–1996. Controls were a random sample of stroke-free, treated hypertensive Group Health Cooperative enrollees (n=2966), similar in age to the stroke cases. Multiple measurements of blood pressure and other cardiovascular risk factors were collected from medical records. Logistic regression was used to estimate the risk of ischemic stroke and hemorrhagic stroke associated with uncontrolled blood pressure, defined as diastolic blood pressure >90 mm Hg or systolic blood pressure >140 mm Hg. The fraction of strokes attributable to uncontrolled blood pressure among treated hypertensives was calculated.

Results—Blood pressure was uncontrolled in 78% of ischemic stroke cases, 85% of hemorrhagic stroke cases, and 65% of controls. After adjustment for potential confounders, uncontrolled blood pressure among treated hypertensive patients was moderately associated with ischemic stroke (risk ratio = 1.5 [95% CI, 1.2 to 1.9]) and strongly related to hemorrhagic stroke (risk ratio = 3.0 [95% CI, 1.7 to 5.4]). We estimated that 27% (95% CI, 11% to 39%) of the ischemic strokes and 57% (95% CI, 26% to 75%) of the hemorrhagic strokes among treated hypertensive patients were attributable to uncontrolled blood pressure. Overall, 32% (95% CI, 14% to 45%) of all strokes were attributable to uncontrolled blood pressure.

Conclusions—A considerable proportion of incident strokes among treated hypertensive patients may be prevented by achieving control of blood pressure. (Stroke. 2000;31:420-424.)

Key Words: hypertension · pharmacology · risk · stroke, hemorrhagic · stroke, ischemic

Although the rates of treatment and control of hypertension in the United States have increased over the past 3 decades, these rates appear to have leveled off during the mid 1990s.1,2 The earlier favorable trends in treatment and control of hypertension coincided with a decline in mortality from stroke and coronary heart disease. However, since 1993, the stroke rate has risen slightly, and the decline in coronary heart disease appears to have leveled off.3 Data from the third National Health and Nutrition Examination Survey (NHANES-III) suggest that only approximately half of those taking antihypertensive drugs achieve blood pressure (BP) levels at or below the treatment goal of 140/90 mm Hg.4 Studies in the United Kingdom and the Netherlands have demonstrated that the quality of control of hypertension is strongly related to the occurrence of stroke in the population.5,6 Using data from a population-based case-control study, we estimated the proportion of incident strokes occurring among treated hypertensive patients that may be attributable to uncontrolled BP in the United States.

Subjects and Methods

Setting

The setting was the Group Health Cooperative of Puget Sound (GHC) in Seattle, a large-staff model health maintenance organization serving >500 000 members in western Washington.

We used data from a population-based case-control study that was originally conducted to study the associations between antihypertensive therapies and myocardial infarction and stroke. Our methods were similar to those used in previous case-control studies.7

Subjects

Cases were GHC enrollees, aged 30 to 79 years, who were treated pharmacologically for hypertension and who sustained an incident
fatal or nonfatal stroke during July 1989 through December 1996. Potential cases were identified from computerized GHC hospital discharge abstracts, Washington state death files, and the billing records for GHC enrollees who received medical care or services from non-GHC providers. Controls were obtained from a companion study of risk factors for myocardial infarction at GHC.7 Controls were a random sample of GHC enrollees who were treated pharmacologically for hypertension, frequency matched to the myocardial infarction cases by sex, age, and calendar year. Each subject was assigned an index date. For the cases, the index date was the date of the stroke; for controls, the index date was a random date within the calendar year for which they had been selected as controls. In most strata based on sex, 10-year age categories, and index year, the ratio of controls to cases was 3:1. We excluded subjects (1) who were enrollees for >1 year or who had <4 visits before their index dates; (2) who had had a prior stroke; (3) who had a diagnosis of congestive heart failure; (4) whose stroke was a complication of a procedure or surgery; and (5) who had no recorded BP in their medical records within the year before the index date.

**Data Collection and Definitions**

Information on BP and other cardiovascular disease risk factors was abstracted from medical records and obtained from a telephone interview of consenting survivors. Abstraction of the information from the medical records was done by trained research assistants who were not blinded to case-control status but were unaware of the study hypothesis. Subjects were considered pharmacologically treated for hypertension when a recording of antihypertensive drug use for the indication of hypertension was present in the medical records and indicated that the subject was treated at the index date. Control of BP was defined according to the mean of the last 3 treated BP readings recorded in the medical records during the year before the index date. If <3 readings were available, we used either the mean of 2 readings (n=563) or a single reading (n=473) to assess the level of BP achieved by treatment.

The level of BP achieved by treatment was categorized according to the classification scheme of hypertension of the sixth report of the Joint National Committee (JNC-VI) on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.4 According to this classification, a diastolic blood pressure (DBP) <90 mm Hg and a systolic blood pressure (SBP) <140 mm Hg are considered controlled. This classification would provide the most informative results for clinicians and policy makers in the United States to assess the implications of managing hypertension according to these national practice guidelines.

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**TABLE 1. Characteristics of Cases and Controls**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls</th>
<th>Ischemic Stroke Cases</th>
<th>Hemorrhagic Stroke Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n*</td>
<td>Mean or %</td>
<td>n*</td>
</tr>
<tr>
<td>Age, y</td>
<td>2966</td>
<td>65.8</td>
<td>460</td>
</tr>
<tr>
<td>Female, %</td>
<td>2966</td>
<td>33.9</td>
<td>460</td>
</tr>
<tr>
<td>Average BP on treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic, mm Hg</td>
<td>2966</td>
<td>144.1</td>
<td>460</td>
</tr>
<tr>
<td>Diastolic, mm Hg</td>
<td>2966</td>
<td>84.2</td>
<td>460</td>
</tr>
<tr>
<td>Pretreatment BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic, mm Hg</td>
<td>2103</td>
<td>162.7</td>
<td>306</td>
</tr>
<tr>
<td>Diastolic, mm Hg</td>
<td>2103</td>
<td>99.4</td>
<td>306</td>
</tr>
<tr>
<td>Duration of treated hypertension, y</td>
<td>2680</td>
<td>11.0</td>
<td>395</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>2820</td>
<td>226.6</td>
<td>439</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>2892</td>
<td>28.5</td>
<td>448</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>2940</td>
<td>12.4</td>
<td>453</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school, %</td>
<td>2214</td>
<td>13.4</td>
<td>267</td>
</tr>
<tr>
<td>High school or vocational school, %</td>
<td>2214</td>
<td>34.6</td>
<td>267</td>
</tr>
<tr>
<td>College or university, %</td>
<td>2214</td>
<td>52.0</td>
<td>267</td>
</tr>
<tr>
<td>Married, %</td>
<td>2966</td>
<td>74.3</td>
<td>460</td>
</tr>
<tr>
<td>White, %</td>
<td>2906</td>
<td>89.5</td>
<td>441</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>2966</td>
<td>11.3</td>
<td>460</td>
</tr>
<tr>
<td>Any cardiovascular disease, %</td>
<td>2966</td>
<td>30.3</td>
<td>460</td>
</tr>
<tr>
<td>History of myocardial infarction, %</td>
<td>2966</td>
<td>8.5</td>
<td>460</td>
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<tr>
<td>History of transient ischaemic attack, %</td>
<td>2966</td>
<td>6.2</td>
<td>460</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>2966</td>
<td>5.3</td>
<td>460</td>
</tr>
<tr>
<td>Angina, %</td>
<td>2966</td>
<td>17.2</td>
<td>460</td>
</tr>
<tr>
<td>Coronary bypass surgery, %</td>
<td>2966</td>
<td>6.0</td>
<td>460</td>
</tr>
<tr>
<td>Coronary angioplasty, %</td>
<td>2966</td>
<td>2.2</td>
<td>460</td>
</tr>
<tr>
<td>Carotid endarterectomy, %</td>
<td>2966</td>
<td>1.0</td>
<td>460</td>
</tr>
<tr>
<td>Peripheral vascular surgery, %</td>
<td>2966</td>
<td>2.3</td>
<td>460</td>
</tr>
</tbody>
</table>

*Number of cases and controls for whom data were available.
†P<.05 for comparison of cases and controls.
Whittemore. 9 We also examined the relation between tertile of DBP attributable fractions and their 95% CIs were calculated according to BP (DBP, of hypertension, 4 compared with the risk in subjects with controlled association between BP control and stroke. We used odds ratios to logistic regression to control for potential confounding factors of the results using multiply-imputed data were similar to those seen in.

In preliminary analyses of demographic and behavioral risk factor data such as smoking, physical activity, race, marital status, and education, the agreement between medical record and self-reported measures was good to excellent. Self-reported data, available for 52.4% of the subjects, were used for these variables; if not available, then data from the medical record were used. After information from these 2 sources was combined, data were missing on smoking (1.0%), physical activity (8.0%), race (2.4%), education (28.1%), cholesterol (5.0%), duration of treatment for hypertension (10.2%), and pretreatment BP (29.7%). We used an approximate Bayesian bootstrap method to impute these missing values. This multiple imputation method is a modification of the hot-deck method and takes account of the imputation variability.8 In sensitivity analyses, the results using multiply-imputed data were similar to those seen in the analysis of subjects with complete data.

All statistical tests were 2-tailed. We used stratification and logistic regression to control for potential confounding factors of the association between BP control and stroke. We used odds ratios to estimate the risk of stroke associated with the various JNC-VI stages of hypertension,4 compared with the risk in subjects with controlled BP (DBP <90 mm Hg and SBP <140 mm Hg). The population attributable fractions and their 95% CIs were calculated according to Whittetmore.9 We also examined the relation between tertile of DBP (bottom tertile, DBP <82 mm Hg; middle tertile, DBP 82 to 90 mm Hg; top tertile, DBP >90 mm Hg) and SBP (bottom tertile, SBP <146 mm Hg; middle tertile, SBP 146 to 159 mm Hg; top tertile, SBP ≥159 mm Hg) and risk of stroke. All analyses were performed separately for ischemic and hemorrhagic strokes.

### Results

During 1989–1996, 791 treated hypertensive patients were hospitalized for or died out of hospital from an incident stroke. We also identified 3654 controls who were eligible. We excluded 38 cases and 149 controls who were enrolled for <1 year or had <4 visits before their index date, 110 cases and 199 controls with chronic heart failure, 17 cases and 64 controls who had no treated BP recorded in their medical records, 60 cases and 289 controls whose most recent BP reading was taken >1 year before the index date, and 23 cases for whom no determination of the type of stroke (ischemic or hemorrhagic) could be made on the basis of the available information. This analysis included 460 ischemic stroke cases, 95 hemorrhagic stroke cases, and 2966 controls.

Compared with controls, ischemic stroke cases had higher mean levels of treated SBP and DBP, were more often current smokers, and more often had a history of transient ischemic attack, but not of cardiovascular disease (Table 1). The mean BP during the year before the index date was more often uncontrolled among ischemic (77.6%) and hemorrhagic (85.3%) stroke cases than among controls (65.3%) (Table 2). Uncontrolled BP was moderately associated with ischemic stroke (risk ratio [RR]=1.52 [95% CI, 1.19 to 1.94]) and strongly related to hemorrhagic stroke (RR=3.03 [95% CI, 1.69 to 5.41]). The relative risks progressively increased with the level of uncontrolled BP defined according to the JNC-VI classification of hypertension, more so for hemorrhagic stroke than for ischemic stroke (Table 2).

The association between both types of stroke and uncontrolled BP did not significantly differ between men and women, between older and younger subjects (above and below the median age), or between subjects with or without a history of cardiovascular disease, with or without diabetes, or with high or low pretreatment DBP or SBP (above and below the median pretreatment BP). The results remained virtually unchanged after adjustment for pretreatment DBP, duration of treated hypertension, body mass index, educational level, marital status,
hemorrhagic stroke cases had a BP
subjects, 78% of the ischemic stroke cases, and 85% of the
before the index date, approximately 65% of the control
population-based study had elevated BP. During the year
pharmacologically treated hypertensive patients in this
In this study we demonstrated that a large proportion of
race, physical activity, and current use of aspirin. Exclusion of
subjects who had <3 BP readings in their medical records
before the index date did not substantially change the results.
Estimation of the population attributable fractions suggests
that 27% (95% CI, 11% to 39%) of ischemic and 57% (95% CI,
26% to 75%) of hemorrhagic strokes may have been attributable
to uncontrolled BP. One third of the ischemic strokes and one
half of the hemorrhagic strokes that were attributable to uncon-
trolled BP occurred among those with mildly elevated BP levels
(JNC-VI stage I). Overall, 32% (95% CI, 14% to 45%) of all
strokes may have been attributable to uncontrolled BP.
The association between ischemic stroke risk and tertile of BP
was similar for DBP and SBP, whereas the risk of hemorrhagic
strokes was more strongly associated with SBP than with DBP
(Table 3).

Discussion
In this study we demonstrated that a large proportion of
pharmacologically treated hypertensive patients in this
population-based study had elevated BP. During the year
before the index date, approximately 65% of the control
subjects, 78% of the ischemic stroke cases, and 85% of the
hemorrhagic stroke cases had a BP >90 mm Hg diastolic or
140 mm Hg systolic. Approximately 27% of incident ische-
mic strokes and 57% of incident hemorrhagic strokes among
pharmacologically treated hypertensive patients were attrib-
tuable to uncontrolled BP. Patients with mild elevations of BP
accounted for approximately one third of the excess incident
ischemic strokes and approximately one half of the excess
incident hemorrhagic strokes.
The strengths of this observational study include the use
of population-based case and control subjects, the compara-
ble ascertainment of potential confounding factors, and
race, physical activity, and current use of aspirin. Exclusion of
subjects who had <3 BP readings in their medical records
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Estimation of the population attributable fractions suggests
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The association between ischemic stroke risk and tertile of BP
was similar for DBP and SBP, whereas the risk of hemorrhagic
strokes was more strongly associated with SBP than with DBP
(Table 3).

### TABLE 3. Risk of Stroke Associated With Tertiles of DBP and SBP Among Pharmacologically Treated Hypertensives

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Ischemic strokes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP &lt;82 mm Hg</td>
<td>176</td>
<td>38.3</td>
<td>1121</td>
</tr>
<tr>
<td>DBP 82–90 mm Hg</td>
<td>175</td>
<td>38.0</td>
<td>1192</td>
</tr>
<tr>
<td>DBP &gt;90 mm Hg</td>
<td>109</td>
<td>23.7</td>
<td>653</td>
</tr>
<tr>
<td>SBP &lt;146 mm Hg</td>
<td>189</td>
<td>41.1</td>
<td>1742</td>
</tr>
<tr>
<td>SBP 146–159 mm Hg</td>
<td>123</td>
<td>26.7</td>
<td>720</td>
</tr>
<tr>
<td>SBP ≥159 mm Hg</td>
<td>148</td>
<td>32.2</td>
<td>504</td>
</tr>
<tr>
<td>Hemorrhagic strokes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP &lt;82 mm Hg</td>
<td>32</td>
<td>33.7</td>
<td>1121</td>
</tr>
<tr>
<td>DBP 82–90 mm Hg</td>
<td>31</td>
<td>32.6</td>
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<td>DBP &gt;90 mm Hg</td>
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<tr>
<td>SBP ≥159 mm Hg</td>
<td>31</td>
<td>32.6</td>
<td>504</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, index year, pretreatment SBP, total cholesterol, diabetes, current smoking,
and clinical cardiovascular disease (diagnoses of angina, claudication, atrial fibrillation, history of
myocardial infarction, transient ischaemic attack, coronary angioplasty, coronary bypass surgery,
carotid endarterectomy, or peripheral vascular surgery).
patients5,15–17 but also provides separate estimates for ischemic and hemorrhagic stroke and the proportion of these strokes that may have been attributable to inadequate control of BP. SBP was more strongly associated with the risk of hemorrhagic stroke than DBP, whereas DBP and SBP were similarly associated with the risk of ischemic stroke. Several studies have found a stronger association between hypertension and hemorrhagic stroke than with ischemic stroke.16–20 However, several studies in Chinese populations have demonstrated a similar risk of ischemic and hemorrhagic stroke in relation to hypertension.21

Previously it was demonstrated in this same population that 15% of the incident myocardial infarctions among treated hypertensive patients were attributable to uncontrolled BP.22 Possible causes of uncontrolled BP include treatment-resistant hypertension,23 recent start of antihypertensive drug therapy, lack of access to medical care,14 suboptimal treatment by physicians, and patient noncompliance. Lack of compliance with antihypertensive drugs24–28 and lack of appropriate treatment29–31 have been identified as the most important barriers to hypertension control. Interventions directed at improvement of compliance32 and optimization of antihypertensive drug treatment33 may lead to improved BP control.

The findings of our study suggest that achieving control of BP among pharmacologically treated hypertensive patients might prevent 57% of hemorrhagic and 27% of ischemic strokes.

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References

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